Physiology and Pharmacology of the Stomach

Introduction

The stomach secretes more than acid—proteases (pepsinogen), lipase, amylases, bicarbonate, mucus, etc. This lesson is about parietal cell regulation of acid secretion. The other secretions don't cause disease and aren't the targets of medical therapy. Acid secretion is the root of GERD, peptic ulcer disease, gastritis, and other diseases we'll discuss in the next lesson. So, for this lesson, we focus on the **regulation of gastric acid secretion**.

Gastric acid secretion, teleologically, should increase when there is food in the stomach, or there is about to be food in the stomach. Vice versa, gastric acid secretion should stop when the stomach is empty. Gastric acid is great for digesting a food bolus into chyme. Gastric acid is also really good at digesting the stomach mucosa and eroding it down to a blood vessel (that's called an ulcer). Our mucosal cells should be able to protect our mucosa with the alkaline mucus they secrete. But if the tide tips too far in favor of acid, the acid will win, and the physiological processes that so efficiently degrade our food bolus will degrade the mucosa, submucosa, and even the muscularis externa.

There are ways, both chemical and neural, to tell the parietal cells to make more acid or stop making acid. These systems can break. These systems can also be targets of pharmacotherapy. We discuss the regulation of gastric acid secretion at the cellular and system levels, then move into pharmacology, saving pathology for the final lesson of the stomach series. This lesson isn't hard, but it is complex.

Regulatory Molecules' Effects on the Parietal Cell

Read this section without Table 5.1 and Figure 5.1. Then read it again after reviewing them.

Parietal cells make gastric acid—hydrochloric acid. They do this through the proton pump on the luminal surface. The proton pump releases a hydrogen ion into the lumen of the stomach and takes back a potassium ion into the cell. That hydrogen ion is generated from carbonic anhydrase. The generation of an H^+ ion requires that a bicarbonate ion (HCO_3^-) be formed. The release of an H^+ ion into the stomach lumen requires the release of the bicarbonate into the blood. This bicarbonate is exchanged for a Cl^- ion on the basolateral membrane. The blood becomes more alkalotic. The Cl^- ion is then allowed to passively diffuse through leak channels into the lumen, where it meets up with H^+ to form the final HCl—stomach acid. The proton pump in the luminal membrane is an **H^+/K^+-ATPase antiporter**—ATP is used to drive H^+ out of the cell and K^+ into the cell, both against their concentration gradients. That proton pump is the one common output of regulation—there is one output, H^+. The parietal cell is heavily regulated by a number of inputs. This section deals only with the inputs to the parietal cell, and what intracellular events they provoke, not where those inputs come from. The subsequent two sections will focus on where these inputs come from and how those inputs are interconnected. At the end, we will discuss medications that antagonize or agonize each receptor.

Parietal cells accept many different inputs, but they all act through only two second-messenger systems, using the same three G protein-coupled receptors (GPCRs) from General Pharmacology. Remember that physiological antagonism is achieved by the stimulation of competing signals. All of these receptors are activated by their ligands. The activation of the receptor leads to competing intracellular events.

Increased calcium stimulates gastric acid secretion. Calcium is increased by the activity of the G_q-IP_3-Ca^{2+} pathway. Two receptors activate the G_q pathway. The first is the **muscarinic M_3 receptor,** which is stimulated by **acetylcholine** from the parasympathetic nervous system—the vagus nerve (or its postganglionic fiber in the submucosal plexus). The second is the **gastrin receptor** (also called CCK_B), which is stimulated by the hormone **gastrin** released from antral G cells. Stimulation of the M_3 or gastrin receptors independently activates G_q, leading to the release of calcium via IP_3 and an increase in gastric acid secretion.

Increased cAMP stimulates gastric acid secretion. cAMP is increased by the activity of the GPCRs that use G_s and is decreased by the activity of the GPCRs that use G_i. Both G_s and G_i influence adenylate cyclase. G_s-AC-cAMP increases adenylate cyclase activity and thus increases the generation of cAMP. G_i-AC-cAMP decreases adenylate cyclase activity and prevents more generation of cAMP. Three receptors involve the cAMP pathway. One, histamine, uses G_s and promotes gastric acid secretion. **Histamine** activates **H_2 receptors**, which in turn **activate G_s** to increase cAMP, thereby increasing acid secretion. Two receptors activate G_i to reduce cAMP and subsequently reduce gastric acid secretion. **Somatostatin** activates the **somatostatin receptor**, thereby **activating G_i** and decreasing cAMP. Finally, **prostaglandins** stimulate the **prostaglandin receptor**, thereby **activating G_i** and **decreasing cAMP**. Decreasing cAMP decreases acid secretion.

MOLECULE	RECEPTOR	G PROTEIN	SECOND MESSENGER	NET EFFECT ON SECRETION
Acetylcholine	M_3	G_q	$\uparrow IP_3/Ca^{++}$	Increase
Gastrin	CCK_B	G_q	$\uparrow IP_3/Ca^{++}$	Increase
Histamine	H_2	G_s	↑cAMP	Increase
Somatostatin	Somatostatin	G_i	↓cAMP	Decrease
Prostaglandin	Prostaglandin	G_i	↓cAMP	Decrease

Table 5.1: Parietal Cells: Receptors and Second Messengers

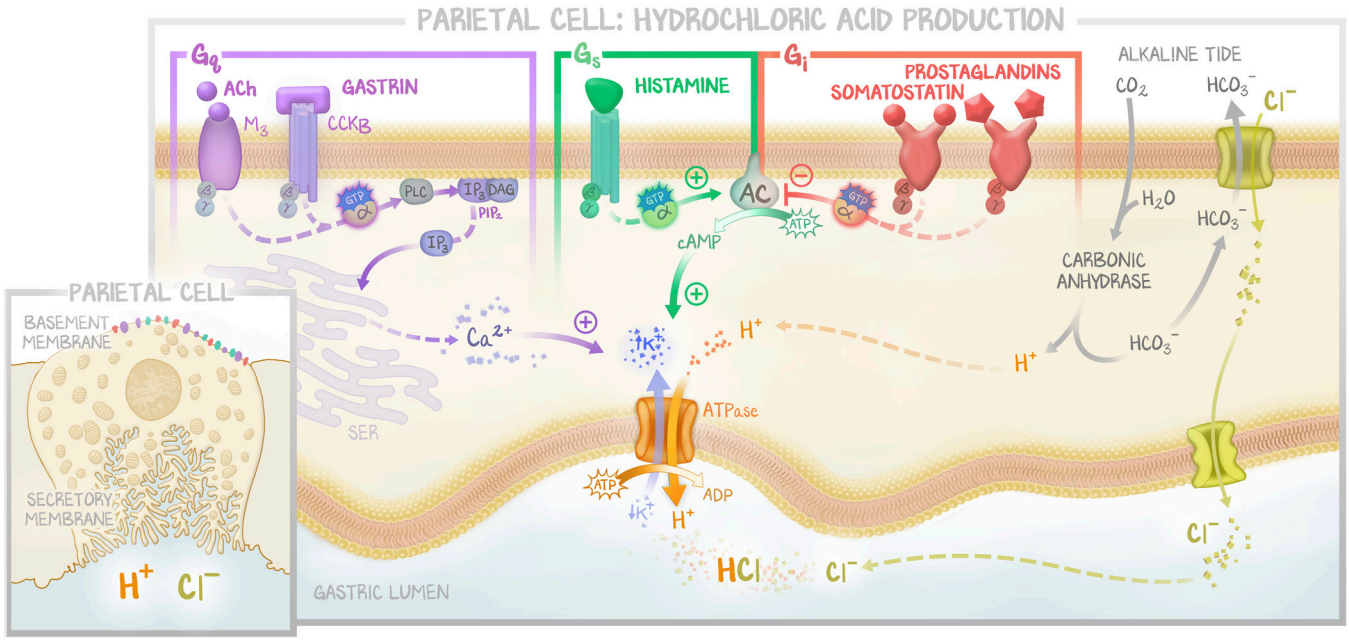

Figure 5.1: Parietal Cells
A summary of the five GPCRs, their intercellular second messengers, and ultimate outcomes on H^+/K^+-ATPase activity. Also shown is the activity of carbonic anhydrase's formation of the H^+ ion and bicarbonate, the exchange of bicarbonate for chloride, and the passive movement of chloride into the lumen. Notice also that all the receptors are oriented towards the basement membrane, towards the lamina propria, towards the blood vessels. Hormones regulate the parietal cells on the basolateral domain. Acid is secreted into the lumen of the apical domain.

Source of and Stimulation to Release Regulatory Molecules: Stomach

Parietal cell regulation is mediated by the vagus nerve to some degree, but it's mostly hormonal. The target of these subsequent regulatory molecules is the parietal cell, but also essentially every other cell that secretes a regulatory molecule. The system has continuous hormonal cross-talk. But although any one signal has multiple targets, every signal has one unique source. This section will link the cell type to the thing it makes, what the primary stimulus to make it is, and what other influences affect its release.

The **G cells** make **gastrin**. Gastrin is secreted into the bloodstream and is, therefore, a hormone. G cells are located in the **antrum** of the stomach. The primary stimulus for G cells is the presence of food in the stomach. Specifically, these cells have apical sensors for the presence of amino acids in the gastric contents; the presence of **tryptophan** or **phenylalanine** stimulates the release of gastrin. In addition, there are vagal inputs and somatostatin. G cells are stimulated to release gastrin by the vagus nerve via the neurotransmitter **GRP** (gastrin-releasing peptide) and NOT via the typical parasympathetic molecule, acetylcholine. Somatostatin from D cells inhibits gastrin secretion.

The **D cells** make **somatostatin**. Somatostatin is secreted into the bloodstream and is, therefore, a hormone. D cells are in the pylorus of the stomach and the duodenum. The D cells' primary stimulus is gastric juice pH. The D cells have luminal receptors for H^+ ions. As the pH falls, H^+ rises, and D cells secrete somatostatin. They are also stimulated by gastrin and inhibited by the vagus nerve. D cells have gastrin receptors, which respond to gastrin from G cells, stimulating somatostatin release—gastrin release stimulates somatostatin release, which inhibits gastrin release. Finally, D cells are **inhibited** by vagus-released **ACh**, so they produce less somatostatin when ACh receptors are activated by the vagus nerve. The only inhibitory signal the vagus delivers is to D cells.

The enterochromaffin cells (**ECL cells**) make **histamine**. We teach histamine as a paracrine signal because its effect is local to the parietal cells of the fundic gland. In truth, ECL cells release histamine into the lamina propria, and it travels as a hormone to local G cells. This histamine does not leave the gland. ECL cells do not measure anything—not pH, not amino acids, not stretch, nothing. They are an added layer of stimulation for parietal cells and are instructed on what to do by all the other neurohormonal inputs. Somatostatin turns them off. Vagal stimulation via ACh and G cell stimulation through gastrin turns them on.

The **vagus nerve** does a lot of things. It can be stimulated by the thought of food (cephalic phase) or by mechanoreceptors in the stomach due to the presence of food (gastric phase) and inhibited by stretching in the duodenum (intestinal phase). It acts through acetylcholine or GRP. Its overall mechanism is to **increase acid production**. It stimulates G cells, ECL cells, and parietal cells. It inhibits D cells.

CELL	THEY MAKE	STIMULATED BY	INHIBITED BY
ECL cells	Histamine	Gastrin Vagal stimulation via ACh	Somatostatin
G cells	Gastrin	Tryptophan and phenylalanine Vagal stimulation via GRP	Somatostatin
D cells	Somatostatin	Gastric pH falling Gastrin	Vagal inhibition via ACh
Vagus	ACh GRP	Cephalic phase Gastric phase (stretch)	Intestinal phase (stretch)
Parietal	Acid	Histamine Gastrin Vagal stimulation via ACh	Somatostatin

Table 5.2: Cells That Regulate Parietal Cell Acid Secretion

Gastrin is a hormone. It circulates through the bloodstream. It stimulates ECL cells to release histamine; histamine stimulates gastric acid secretion. Gastrin stimulates parietal cells directly, stimulating gastric acid secretion. Gastrin also **stimulates D cells**, which secrete somatostatin, which inhibits ECL cells, G cells, and parietal cells. This is a fail-safe against gastrin overproduction. Gastrin turns on all the mechanisms of acid secretion AND turns on the somatostatin (the only acid secretion inhibitor signal).

Histamine is a paracrine ligand released near the parietal cells by ECL cells. It stimulates parietal cells to make acid. It only functions locally and influences only parietal cells.

Somatostatin is a hormone. It circulates through the bloodstream. It inhibits ECL cells, inhibits G cells, and inhibits parietal cells. It sends all of the cells into "**somatostasis**."

The **vagus nerve** stimulates G cells via GRP. This increases the gastrin signal in the gastrin paragraph above. The vagus nerve stimulates ECL cells via ACh. This increases the histamine signal. The vagus nerve stimulates parietal cells directly with ACh, increasing gastric acid secretion. The vagus nerve **inhibits D cells via ACh,** thus inhibiting the somatostatin signal from D cells, therefore disinhibiting the system.

MOLECULE	SIGNALING	ACTION	RESULT
Gastrin	Endocrine	Stimulates parietal cells Stimulates ECL cells Stimulates D cells	↑ Gastric acid ↑ Gastric acid (histamine) ↓ Gastric acid (somatostatin)
Histamine	Paracrine	Stimulates parietal cells	↑ Gastric acid
Somatostatin	Endocrine	Inhibits parietal cells Inhibits ECL cells Inhibits G cells	↓ Gastric acid ↓ Gastric acid (↓ histamine) ↓ Gastric acid (↓ gastrin)
GRP	Paracrine	Stimulates G cells	↑ Gastric acid (gastrin, gastrin-histamine)
ACh	Paracrine	Stimulates parietal cells Stimulates ECL cells Inhibits somatostatin	↑ Gastric acid ↑ Gastric acid (histamine) ↑ Gastric acid (↓somatostatin)

Table 5.3: Molecules That Regulate Parietal Cells
The molecules, what type of chemical signaling is used, which cells the molecule stimulates, and the net result on acid secretion.

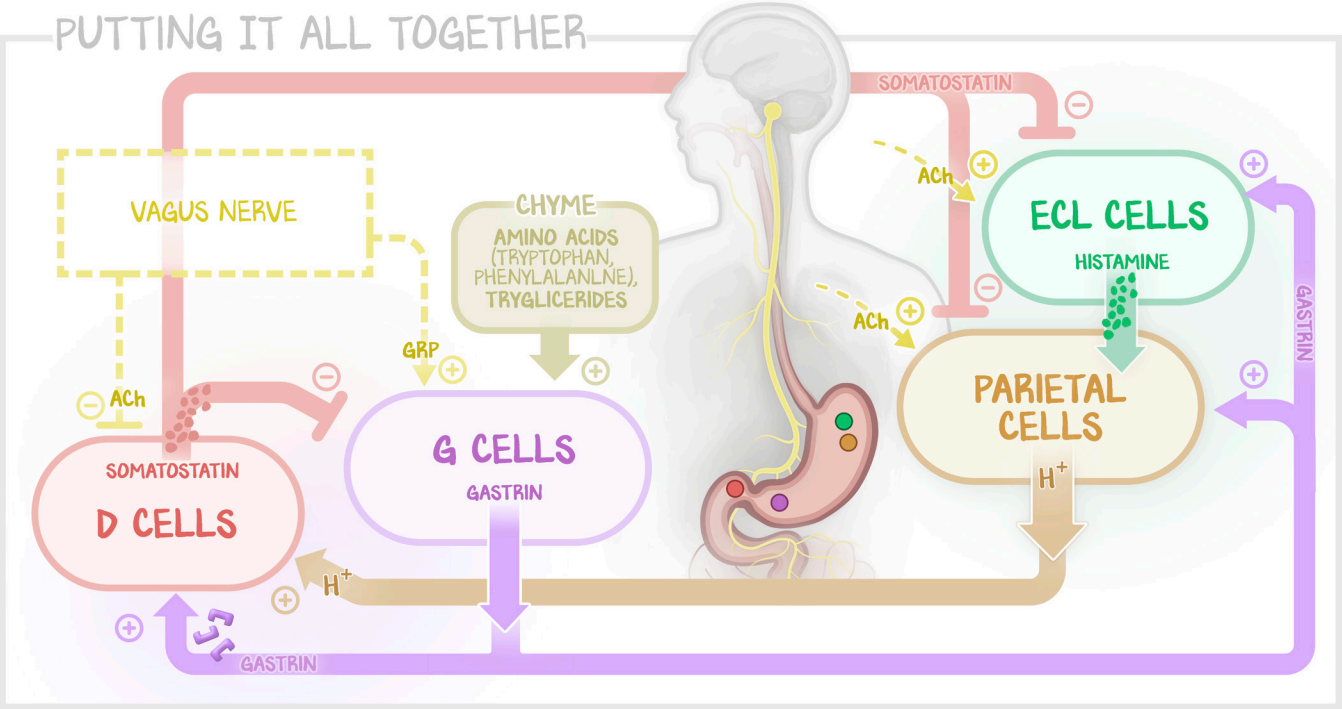

Figure 5.2: Putting It All Together
When you can draw this image from memory, you have mastered this information. At that point, the preceding pages may seem tedious. But figuring it out takes a lot of effort.

Source of and Stimulation to Release Regulatory Molecules: Duodenum

As if gastric acid regulation wasn't already hard enough, there are even more signals that come from the duodenum. But good news, most of the signals from the duodenum are NOT to the stomach, but to the gallbladder and pancreas. Most of the signals are "give me digestive enzymes, yo," and not "stop making acid, stomach." These do matter to normal physiology, and they are present primarily in the proximal duodenum (which is why losing it to pancreatic cancer causes so many problems).

The stomach's job is to churn and digest food into chyme. Physiological systems stimulate receptors. So most of the signals discussed in the previous section increase gastric acid secretion. The role of the duodenum is to absorb the chyme and turn off the stomach. Most of these signals are going to be stimulated as a result of the stomach doing what it does, and most of these signals will turn off the stomach's doing what it does—gastric acid secretion.

These signals are sent **from the duodenum**. There are multiple sensors and multiple outputs. **Distension** of the duodenum results in a mechanoreceptor-mediated vagovagal response (**neural reflex**), which inhibits the release of ACh and GRP. This removes the feedforward signal from the vagus nerve onto the stomach. The "go" signal is turned off. The rest of the intestinal responses are together summed as **enterogastrones**, hormones released from the duodenum that stimulate either the inhibition of gastric acid secretion, or the things that help neutralize the gastric acid in the duodenum.

CELL	THEY MAKE	WHAT THEY DO	WHAT STIMULATES THEM
D cells	Somatostatin	Somatostasis everywhere, pancreas, GB, stomach	Low pH (like in antrum)
I Cells	Cholecystokinin (CCK)	↑ Pancreatic secretions ↑ GB contraction ↓ Gastric emptying	Fatty acids, low PH
S Cells	Secretin	↑ Pancreatic bicarb excretion ↓ Gastric acid secretion	Fatty acids, low pH
K Cells	Gastric inhibitor hormone (GIP)	↓ Gastric acid secretion	Fatty acids, amino acids
Sphincters	Vasoactive intestinal peptide (VIP)	Relaxes sphincters	Distension

Table 5.4: Duodenal Regulation of Parietal Cells and the Other Stuff They Do

Phases of Eating

The **cephalic phase** happens before you eat. This is the phase where you think you might eat (you see, smell, or think of food). Regulation of the cephalic phase can only be through the vagus nerve, because there is no physical food in the stomach, and the vagus comes from your brain. You salivate, gastric secretions turn on, and you pump out acid. Because there is nothing in the lumen to buffer the acid you're making, the luminal pH is the only limit to acid production. The vagus nerve stimulates ECL cells, G cells, and parietal cells while inhibiting somatostatin. The stomach is preparing to be delivered a food bolus. If none comes, as the pH falls, D cell's primary stimulus—low pH—overcomes the vagal signal, and somatostatin overcomes the vagus. This prevents too much acid from being secreted if you end up not eating.

In the **gastric phase**, when the meal is done, and food is in the stomach, three direct stimuli occur. First, as food fills the stomach, mechanoreceptors discharge in response to stretching. Both the afferent and efferent limbs are coordinated by the vagus nerve; therefore, this is called a **vagovagal response** (vagus-vagus). This vagovagal response is the same as the vagal response in the cephalic phase—inhibit D cells, stimulate everything else. Second, G cells sample the chyme and increase their gastrin production if amino acids are found. Third, D cells sample gastric content for pH. Food acts as a buffer to the pH. When the food bolus, which has a higher pH than the gastric acid does, is added to the gastric acid, the net pH rises. Because low pH activates D cells' H^+ receptors, buffering the pH to be higher reduces the signal to release somatostatin, which in turn results in a disinhibition of gastric acid secretions.

In the **intestinal phase**, chyme is out of the stomach and in the intestine. Fatty acids, low pH, amino acids, and distension all happen. The neural reflex is to silence the vagus nerve. The enterogastrones inhibit gastric acid secretion and promote the neutralization of the contents in the duodenum.

Pharmacology of Gastric Acid Secretion

H_2 receptor antagonists. The drugs in this class are cimetidine and famotidine (the very popular OTC ranitidine was pulled from the market in 2020); the "-tidine" drugs are H_2 blockers. They are **competitive inhibitors** for the histamine receptor, preventing the binding of histamine, and thereby preventing the G_s signal and subsequently reducing cAMP. Reduced cAMP results in less ATPase activity and reduced H^+ secretion. These are old drugs, now available over the counter and used to treat GERD. They can be used to treat peptic ulcer disease and gastritis as well, although proton pump inhibitors have gained favor.

They are also used **prophylactically in the ICU** in ventilated patients to prevent stress-induced ulcers (non-fed, ventilated, increased intracranial pressure, and burn patients are at the highest risk). Side effects are generally mild. Even though NO ONE will ever use cimetidine because only cimetidine has the following side effects, cimetidine is commonly tested on licensing exams. Cimetidine is a **P450 inhibitor** and **competes for renal PGP**. This means that when you take cimetidine, the effective dose of other drugs metabolized by P450 or excreted by the kidneys will be increased (so, close to all of them). This particularly involves warfarin. Cimetidine also has anti-androgen effects, so it may cause **gynecomastia** in men and **galactorrhea** in women. It also crosses the blood-brain barrier and can have neurologic side effects. All of the other H_2 blockers have none of these consequences.

Proton pump inhibitors. The "-prazole" drugs are PPIs (be careful, because antifungals also end in "-azole"). They are **noncompetitive inhibitors** for the **proton pump**, which they **irreversibly inhibit**. Because they irreversibly inhibit the proton pump itself, it doesn't matter what signals are stimulating the parietal cell—the final output is blocked. They are now the mainstay for treating diseases involving acid secretion: **GERD and ulcers**. They are also useful in treating diseases where there is an upregulation of receptors, either those for which we do not have antagonists or those for which we have competitive antagonists, such as **Zollinger-Ellison syndrome** (a pancreatic tumor secreting gastrin). This is the drug class that was used in all hospitalized patients for stress ulcer prophylaxis. And it worked. Ulcer incidence went down. But oops, it turns out the number needed to treat for stress ulcers was higher than the number needed to harm for *C. diff*. PPIs significantly increase the risk of *C. diff* infections in hospitalized patients and the community. PPIs also increase the risk of pneumonia. Because gastric acid is intended to kill pathogens in the GI tract as well as digest food, it is likely (though not proven) that, by inhibiting gastric acid, PPIs may also impair its sterilization effect. PPIs also cause impaired calcium absorption, which can lead to osteoporosis later in life. Because D cells look for low pH, and PPIs silence that signal, somatostatin release is impaired. This has a meaningful effect on gastrin levels, which will be elevated. Gastrin levels are normally in the double digits. Zollinger-Ellison gastrin levels are in the thousands. Gastrin levels on PPIs are in the hundreds. Drugs in this class include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, and pantoprazole.

Antacids. Calcium carbonate neutralizes stomach acid. It is fast-acting but temporary. Antacids are useful for heartburn symptoms in the moment but do nothing long-term.

Sucralfate, bismuth. These drugs are used as adjuncts in ulcer treatment. They coat the base of the ulcer. An ulcer is the loss of the protective mucosa. These drugs coat the ulcer so that layer can be regenerated from the stem cells below. Bismuth turns the stool black. Because ulcers can cause a GI bleed and will present with melena (which is black), counseling patients that bismuth is the cause of their black stool is helpful. Other than "forming a protective coat," the exact mechanism is uncertain for both of these drugs.

Prostaglandins = misoprostol. Activation of prostaglandin receptors not only **directly inhibits acid secretion** via activation of G_i but also **stimulates mucus secretion**. That means they turn down the damaging stuff, but turn up the protective stuff. They are particularly useful in patients that have killed their mucosal defense; they are used to treat **ulcers from NSAID use**. Because the use of NSAIDs reduces prostaglandin synthesis, by administering prostaglandins, you are essentially replacing the prostaglandins. Misoprostol also happens to be an abortifacient, so pregnant females should not use misoprostol. This is essentially no longer considered a treatment for acid secretion disorders, but it illustrates the physiology well, so it remains tested. In 1990, H_2 blockers were found to be obviously better than prostaglandin analogs. Prostaglandin analogs are still taught for the physiology and history of pharmacology.

Antimuscarinics. Even more old school than prostaglandin analogs are drugs like pirenzepine, an atropine derivative, which would theoretically work if the side effects of systemic antimuscarinics were

not so amazingly impractical. Before the advent of PPIs, vagotomy was a surgical treatment for ulcers, which is a permanent and surgical "antimuscarinic." PPIs render these therapies futile. They are included for completeness and as a reminder of what we, as a medical community, have previously tried.

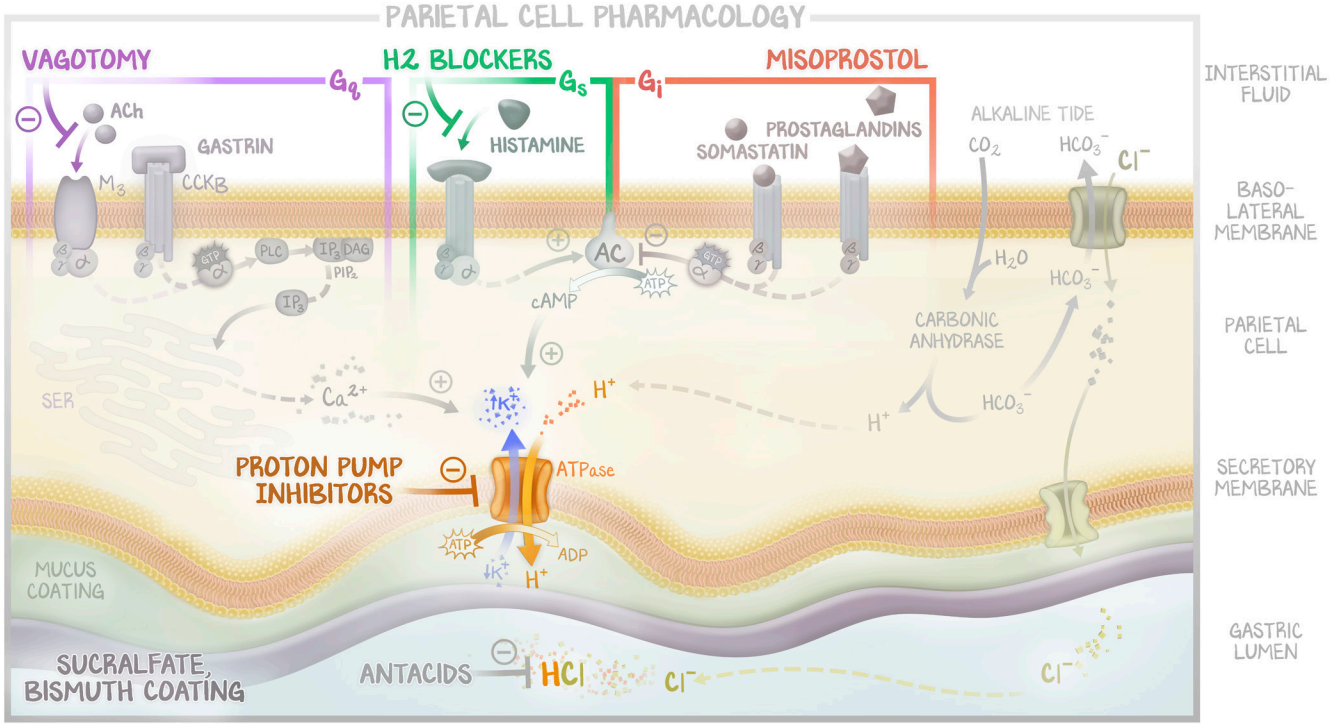

Figure 5.3: Parietal Cell Pharmacology
Summary slide of the parietal physiology, the receptors, and how the medications influence that system. Sucralfate and bismuth coat the mucosa (represented here by the apical surface of the parietal cell, but you know it means surface cells and gastric pits). Antacids neutralize the H^+ in the lumen, but only act temporarily. Proton pump inhibitors irreversibly prevent the production of H^+ ions. The other treatments target the GPCRs of parietal cell regulation. Notice that somatostatin and gastrin do not have medications associated with them.

CLASS	NAMES	MECHANISM	SIDE EFFECTS
Proton pump inhibitors	Omeprazole Pantoprazole Lansoprazole	Apical H^+/K^+ transporter antagonist	Hypocalcemia *C. diff* colitis Pneumonia Hypergastrinemia
H_2 blockers	Famotidine	Basolateral H_2 receptor antagonist	
Prostaglandins	Misoprostol Arbaprostil	Basolateral PGE_2 receptor agonist	Abortifacient
Antacids	Calcium carbonate Aluminum carbonate	Are alkaline	Hypercalcemia
Sucralfate, bismuth	Sucralfate, bismuth	Coats base	Stool turns black

Table 5.5: Medications Used to Treat Stomach Acid